IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al.

Serial No.: To be assigned (National Phase of PCT/GB03/02557 filed June 13, 2003)

Filed: December 14, 2004

For: COMBINATION OF AZELASTINE AND STEROIDS

NOTICE OF CLAIM FOR PRIORITY

Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The benefit of the filing date of the following prior foreign application filed in the following foreign country is hereby requested for the above-identified application and the priority provided in 35 USC 119 is hereby claimed:

Great Britain Appln. No. 0213739.6, Filed 14 June 2002 .

It is requested that the file of this application be marked to indicate that the requirements of 35 USC 119 have been fulfilled and that the Patent and Trademark Office kindly acknowledge receipt of this document.

Respectfully submitted,

Date: Dec 14, 2004 By: _____
Registration No. 31,674

TPP/pgw
ATTORNEY DOCKET NO. TPP31753

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P01/7700 0.00-0213739.6

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14 JUN 2002

The Patent Office

Cardiff Road
Newport
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NP9 1RH

1. Your reference — CPW/20632

14 JUN 2002

2. Patent application number *(The Patent Office will fill in this part)* — 0213739.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if you know it)* 7739162001

If the applicant is a corporate body, give the country/state of its incorporation — INDIA

4. Title of the invention — PHARMACEUTICAL COMPOSITIONS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)* 0000075001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

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11. I/We request the grant of a patent on the basis of this application.

Signature A. A. Thornton Date 14/6/02

A. A. Thornton & Co. 14th June 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Philip A. Curtis - 020 7440 6860

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PHARMACEUTICAL COMPOSITIONS

This invention relates to pharmaceutical compositions. More particularly this invention relates to pharmaceutical compositions useful for preventing or minimising allergic reactions. More particularly, but not exclusively, this invention relates to pharmaceutical compositions for nasal and ocular use.

Such allergic reactions commonly comprise the allergy-related and vasomotor-related symptoms and the rhinovirus-related symptoms.

It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine azelastine (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.

It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, fluticasone, budesonide and cyclosenide. Corticosteroids known for ocular anti-inflammatory use include betamethasone sodium, dexamethasone sodium and prednisolone acetate, for example.

It would be highly desirable, however, to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments, in a pharmaceutically acceptable composition, which is tolerated *in situ*, without significantly disrupting the potency of the constituent pharmaceuticals.

We have now found that, very surprisingly, azelastine (4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone) , or a salt thereof, can advantageously be combined with a steroid to provide a stable, very effective combination composition for nasal or ocular treatment. The combination provides, in a single administration, the antihistaminic properties of azelastine and the anti-inflammatory (and/or other) properties of the steroid, without any significant interference between the two, or adverse reaction *in situ*.

In one aspect the invention provides a pharmaceutical composition comprising azelastine or a salt thereof and a steroid, preferably a corticosteroid, the composition being in a form suitable for administration nasally or ocularly.

The preferred forms of compositions of the invention are nasal drops, eye drops, nasal sprays, nasal inhalation solutions or aerosols or insufflation powders.

Preferred embodiments of the invention comprise stable aqueous solutions of azelastine or one or more of its salts, in combination with steroids which may be beclomethasone, mometasone, fluticasone, budesonide or cyclosenide, which can be used in the form of inhalation solution, pressurized aerosol, eye drops or nasal drops, and in a particular preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can, for example, be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. In a preferred embodiment, 0.03 to 3 mg of azelastine base and 0.05 to 0.15 mg of the steroid should be released per individual actuation.

The compositions preferably contain a preservative and/or stabilizer. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and its alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl-butyl)phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05%, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride".

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is preferably from 0.001 to 0.10g, preferably 0.01g per 100ml of solution/suspension or 100g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used: thimero sal 0.002-0.02%; benzalkonium chloride 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;); chlorhexidine acetate or gluconate 0.01 to 0.02%; phenyl mercuric/nitrate, borate, acetate 0.002-0.004%; p-hydroxybenzoic acid ester (for example, a mixture of the methyl ester and propyl ester in the ratio 7:3): preferably 0.05-0.15, more preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example, as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is preferably used in a concentration of 0.05 to 0.1%, benzalkonium chloride preferably being used in a concentration of 0.005 to 0.05%, more preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerisation of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine component.

It is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50 to 0.56 degree C is attained in comparison to pure water.

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example: Glucose $1H_2O$ 3.81g; saccharose 6.35g; glycerine 2.2g; 1,2-propylene glycol 1.617g; sorbitol 3.84g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.

Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight of the formulation, for example, is used for this purpose.

In the event of the use of Avicel RC 591 or CL11, 0.65-3.0% by weight of the composition, for example, is used for the purpose.

It is also possible to add to the formulations buffer substances such as citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), trometamol or equivalent conventional buffers in order, for example, to adjust the formulations to a pH value of 3 to 7, preferably 4.5 to 6.5.

The amount of citric acid is, for example, 0.01 to 0.14g, preferably 0.04 to 0.05g, the amount of disodium hydrogenphosphate 0.1 to 0.5g, preferably 0.2 to 0.3g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer is preferably less than 5%, in particular less than 2% (weight/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in combination with steroid, in the form of a solution or suspension in a so-called propellant. The propellant may be a pressurized liquid chlorinated, fluorinated hydrocarbon or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutene or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. Hydrofluorocarbons (HFCs), such as HFC 134a, can also be used, if desired. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed in the nose or which are available for inspiration into the nose. Certain plastic applicators may be used to actuate the valve and to convey the sprayed suspension into the nose.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

In the case of insufflatable powder, the maximum particle size of the substance preferably does not exceed 10μm. Azelastine or its salts and the steroid may be mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc.

In one embodiment, the steroid has a particle size of less than about 10μm, preferably less than 5 μm.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

EXAMPLE 1

Nasal spray or nasal drops with 0.1% azelastine hydrochloride as active ingredient and steroid 0.1%

S.NO.	NAME OF INGREDIENTS	OUANTITY %w/v
1. *	Azelastine hydrochloride	0.1%
2.	Steroid	0.1%
3.	Disodium edetate	0.005%
4.	Sodium chloride	0.9%
5.	Benzalkonium chloride	0.001%
6.	Avicel RC 591	1.2%
7.	Citric acid monohydrate	0.2%
8.	Disodium hydrogen phosphate dodecahydrate	0.1%
9.	Purified water	

EXAMPLE 2

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride and 50 micrograms of Beclomethasone dipropionate freon solvate per stroke.

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about –55 degree C in an appropriate cooling vessel. A mixture of 0.086 kg of pre-cooled sorbitantrioleate and 0.8600 kg of pre-cooled trichlorofluoromethane are dissolved with stirring into the mixture at –55 degrees C, 0.0688 kg of micronized azelastine hydrochloride, 0.00688 kg of Beclomethasone dipropionate freon solvate and 0.0688 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about –55 degree C.

Following closure of the cooling vessel the suspension is again cooled to about -55 degrees C under intensive stirring. It is then ready to be filled.

CLAIMS:

1 A pharmaceutical composition which comprises azelastine or a salt thereof, and a steroid, the composition being in a form suitable for nasal or ocular administration.

2 A composition according to claim 1, which is an aqueous suspension or solution.

3 A composition according to claim 1 or 2, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray or an inhalation solution.

4 A composition according to claim 1, which is in the form of an insufflation powder.

5 A composition according to any of claims 1 to 4, wherein the steroid is beclomethasone or an ester thereof, mometasone or an ester thereof, fluticasone or an ester thereof, budesonide or cyclosenide, in any chiral form or mixture.

6 A composition according to claim 5, wherein the steroid is beclomethasone propionate, mometasone furoate or fluticasone propionate.

7 An composition according to any of claims 1 to 6, which contains the steroid in an amount from about 50 micrograms/ml to about 5 mg/ml of the composition.

8 A composition according to any of claims 1 to 7, which is a suspension containing 0.0005 to 2% (weight/weight of the composition) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the composition) of said steroid.

9 A composition according to claim 8, which contains from 0.001 to 1% (weight/weight of the composition) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the composition) steroid.

10 A composition according to any of claims 1 to 9, wherein the composition has a particle size of less than about 10μm, preferably less than 5 μm.

11 A composition according to any of claims 1 to 10, which also contains a surfactant.

12 A composition according to claim 11, wherein the surfactant comprises a polysorbate or poloxamer surfactant.

13 A composition according to claim 10 or 11, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the composition.

14 A composition according to any of claims 1 to 13, which also contains an isotonic agent.

15 A composition according to claim 14, wherein the isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

16 A composition according to any of claims 1 to 15, which also contains at least one of a buffer, a preservative and a suspending or thickening agent.

17 A composition according to claim 16, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorohexidine, phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof.

18 A composition according to claim 16 or 17, wherein the suspending agent or thickening agent is selected from cellulose derivatives, gelatine, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin.

19 A composition according to claim 16, 17 or 18, wherein the buffer comprises a citric acid-citrate buffer.

20 A composition according to claim 16, 17, 18 or 19, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7, preferably 4.5 to about 6.5.

21 An aqueous pharmaceutical composition substantially as herein described in Example 1 or 2.

22 A method of treating irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes, a medicament which contains a member selected from the group consisting of azelastine and its pharmaceutically acceptable salts, in combination with a steroid.

23 A method according to claim 22, in which the medicament is a composition as claimed in any of claims 1 to 21.

24 A method of treating airway disorders, comprising administering by nebulization to surfaces of the airway a treatment-effective amount of a composition as claimed in any of claims 1 to 21.